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(56) Documents cited
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(58) Field of search
C2C

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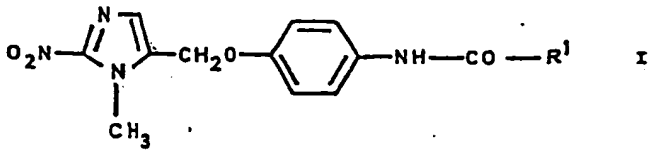
(54) **2-nitroimidazoles**

(57) 2-Nitroimidazoles having protozoocidal activity of the general formula



I

wherein R^1 signifies 1-methyl-2-pyrrolidinyl or a group $-CH_2-NR^2R^3$ in which R^2 and R^3 each represent C_{1-4}-alkyl or $-NR^2R^3$ is the residue of a five-membered or six-membered saturated heterocyclic ring system which optionally contains a further nitrogen or oxygen atom in the ring.

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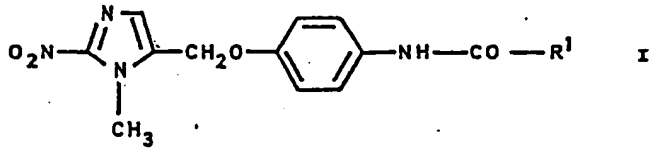

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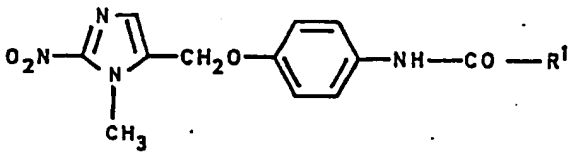
SPECIFICATION

2-Nitroimidazoles

The present invention is concerned with novel 2-nitroimidazoles of the general formula



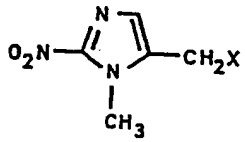
I

wherein R^1 signifies 1-methyl-2-pyrrolidinyl or a group $-CH_2-NR^2R^3$ in which R^2 and R^3 each represent C_{1-4}-alkyl or $-NR^2R^3$ is the residue of a five-membered or six-membered saturated heterocyclic ring system which optionally contains a further nitrogen or oxygen atom in the ring,
and physiologically acceptable acid addition salts thereof. The invention also comprises a process for the manufacture of these novel compounds, pharmaceutical preparations containing them as well as the use of these compounds as medicaments.

The C_{1-4}-alkyl groups can be straight-chain or branched-chain; methyl and ethyl are preferred. Examples of five-membered or six-membered heterocyclic ring systems which optionally contain a further nitrogen or oxygen atom in the ring are pyrrolidine, piperidine, piperazine and morpholine.

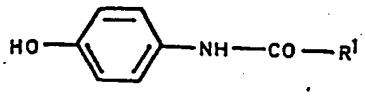
The process provided by the present invention comprises

(a) reacting a compound of the formula



II

wherein X represents hydroxy, chlorine, bromine or iodine,
with a compound of the formula



III

wherein R^1 has the significance given earlier,
or

(b) reacting a 2-halo-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide with a compound of the formula HNR^2R^3 in which R^2 and R^3 have the significance given earlier, or

(c) reacting α-(1-methyl-2-nitroimidazol-5-yl)-p-anisidine with a compound of the formula R^1-COOH in which R^1 has the significance given earlier or a reactive derivative thereof and, if desired, converting a compound of formula I obtained into a physiologically acceptable acid addition salt.

Process variants (a), (b) and (c) are condensation reactions which can be carried out within the framework of usual conditions which are familiar to a person skilled in the art, i.e. in one of the known inert solvents, at temperatures between room temperature and the reflux temperature of the reaction mixture, if desired in the presence of a condensation agent. As reactive derivatives of compounds of the formula R^1-COOH used in process variant (c) there come into consideration, for example, acid halides or anhydrides.

The novel 2-nitroimidazoles provided by the present invention exhibit protozoocidal, especially trypanosomicidal, activity. Compared with known compounds which have recognized good trypanosomicidal activity such as, for example, pentamidine or suramin they are distinguished excellent fluid passability, while compared with already known 2-nitroimidazoles which have the same direction of activity such as, for example, benznidazole or misonidazole they are distinguished by substantially stronger activity against African trypanosomes (e.g. Trypanosoma rhodesiense which causes sleeping sickness) (see Table 1).

A preferred field of use for the compounds provided by the present invention is in veterinary medicine, namely where trypanosome diseases play a significant role. Nagana (caused by T. congolense, T. vivax, T. brucei), surra (caused by T. evansi) and dourine (t. equiperdum) are prominent diseases of this type.

TABLE 1

Compound	ED_{50}[mg/kg], T.rhodesiense p.o.
Misonidazole	400
Benznidazole	400
2-(Dimethylamino)-α-(1-methyl-2--nitroimidazol-5-yl)-p-acetanisidide	3
2-(Dimethylamino)-α-(1-methyl-2--nitroimidazol-5-yl)-p-acetanisidide	17
2-(Dibutylamino)-α-(1-methyl-2--nitroimidazol-5-yl)-p-acetanisidide	90
α-(1-Methyl-2-nitroimidazol-5-yl)--1-pyrrolidine-p-acetanisidide	2.7
α-(1-Methyl-2-nitroimidazol-5-yl)--1-piperidine-1-acetanisidide	55
α-(1-Methyl-2-nitroimidazol-5-yl)--4-morpholine-p-acetanisidide	30
(2S)-1-Methyl-α-(1-methyl-2-nitro-imidazol-5-yl)-pyrrolidine-carboxy--p-anisidide	18

The compounds provided by the present invention can therefore be used as medicaments, namely for the prophylaxis and therapy of illnesses caused by protozoa, especially trypanosomes, such as sleeping sickness. They can be administered in the form of solid or liquid pharmaceutical preparations in admixture with organic or inorganic inert carrier materials suitable for oral or parenteral administration as well as the usual adjuvant substances. An amount of 1-10 mg of active substance/kg body weight per day during a treatment period of 1-10 days can be regarded as the dosage guideline in the case of human beings. The dosage unit conveniently lies at 50-1000 mg. An analogous dosage also applies in veterinary medicine.

The compounds of formula I provided by the present invention can be present in the pharmaceutical preparations in the form of their acid addition salts with known physiologically compatible acids (e.g. hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, citric acid or tartaric acid). These salts can be prepared by reacting the compounds of formula I with the desired acid in a manner known per se.

The manufacture of the compounds provided by the present invention is illustrated by the following Examples.

Example 1

78.5 g of 1-methyl-2-nitroimidazole-5-methanol were suspended in 1.5 l of anhydrous tetrahydrofuran. After the addition of 102 g of p-chloroacetylaminophenol and 144 g of triphenylphosphane, the mixture was cooled to 10°C and a solution of 111 g of diisopropyl azodicarboxylate in 750 ml of anhydrous tetrahydrofuran was added thereto with strong stirring within 20 minutes, the temperature being held at 10-12°C by means of an ice-bath. The mixture was stored in a refrigerator overnight and the crystalline precipitate was filtered off under suction. After recrystallization from 2 l of acetonitrile, there were obtained 90.9 g (56.6%) of pure 2-chloro-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide, m.p. 192-194°C (decomposition).

32 ml of a 3.68 molar solution of dimethylamine in ethanol were added to a suspension of 20 g of the foregoing anisidide in 500 ml of ethanol. The mixture was boiled under reflux for 5 hours, concentrated to dryness under reduced pressure and taken up with 1 l of methylene chloride and 400 ml of water. The mixture was adjusted to pH 7 with sodium bicarbonate. The organic phase was then separated, washed with a small amount of water and evaporated. By crystallization of the residue from 200 ml of isopropanol there were obtained 16.6 g (82%) of 2-(dimethylamino)-α--(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide, m.p. 128-129°C.

15 g of 2-(dimethylamino)-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide were dissolved in 300 ml of hot ethanol. 12 ml of 4.1N ethanolic hydrochloric acid were added dropwise thereto while stirring, the mixture was cooled in an ice-bath and 250 ml of diethyl ether were added thereto. After leaving to stand in a refrigerator overnight, the precipitated hydrochloride was filtered off under suction, washed with diethyl ether and dried in vacuo. There were obtained 16.4 g of 2-(dimethylamino)-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide hydrochloride, m.p. 193-194°C (decomposition).

Example 2

7 g of 2-chloro-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide and 3.8 g of pyrrolidine were heated under reflux for 5 hours in 200 ml of ethanol. The mixture was concentrated to about 50 ml and cooled. Recrystallization of the precipitate from acetonitrile yielded 5.9 g (76%) of α-(1-methyl-2-nitroimidazol-5-yl)-1-pyrrolidine-p-acetanisidide, m.p. 141-143°C.

15 g of α-(1-methyl-2-nitroimidazol-5-yl)-1-pyrrolidine-p-acetanisidide were dissolved in 350 ml of hot ethanol. 11 ml of 4.1N ethanolic hydrochloric acid were added dropwise thereto while stirring, the mixture was cooled in an ice-bath and 250 ml of diethyl ether were added thereto. After leaving to stand in a refrigerator overnight, the precipitated hydrochloride was filtered off under suction, washed with diethyl ether and dried in vacuo. There were obtained 15.4 g of α-(1-methyl-2-nitroimidazol-5-yl)-1-pyrrolidine-p-acetanisidide hydrochloride, m.p. 209-210°C (decomposition).

Example 3

In a manner analogous to Example 2, from 4.6 g of piperidine there were obtained 6.1 g (75%) of α-(1-methyl-2-nitroimidazol-5-yl)-1-piperidine-p-acetanisidide, m.p. 162-163°C.

Example 4

In a manner analogous to Example 2, from 3.95 g of diethylamine there were obtained 5 g (64%) of 2-(diethylamino)-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide, m.p. 106-108°C (from toluene).

Example 5

In a manner analogous to Example 2, from 3.24 g of 2-chloro-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide and 2.18 g of morpholine there were obtained 3.3 g (83%) of α-(1-methyl-2-nitroimidazol-5-yl)-4-morpholine-p-acetanisidide, m.p. 154-156°C (from methanol).

Example 6

A suspension of 30 g of 1-methyl-2-nitroimidazole-5-methanol, 22 g of 4-aminophenol and 55 g of triphenylphosphane in 600 ml of anhydrous tetrahydrofuran was treated dropwise while stirring strongly within 20 minutes with a solution of 42.5 g of diisopropyl azodicarboxylate in 300 ml of anhydrous tetrahydrofuran. The mixture was held at a temperature of 20-24°C by external cooling. After 2 hours, the clear solution obtained was evaporated under reduced pressure and the residue was boiled up briefly with a mixture of 125 ml of methylene chloride and 125 ml of ethyl acetate. There were obtained 24.4 g (52%) of crystalline α-(1-methyl-2-nitroimidazol-5-yl)-p-anisidine, m.p. 168-170°C.

A solution of 4.14 g of N-methyl-L-proline and 6.2 g of the foregoing anisidine in 250 ml of acetonitrile was treated with 12.5 ml of triethylamine and subsequently with 8.5 g of 2-fluoro-1-methylpyridinium tosylate. The mixture was heated under reflux for 1 hour, the solvent was removed under reduced pressure and the residue was partitioned between 200 ml of ethyl acetate and 200 ml of water. The aqueous phase was adjusted to pH 10 with sodium hydroxide and extracted three times with 100 ml of ethyl acetate each time. The combined extracts were evaporated. The residue was filtered over 28 g of silica gel with acetone/toluene (1:1, v/v). After a forerun of 350 ml, from the next 2000 ml of the eluate there were obtained 8.1 g of (2S)-1-methyl-α-(1-methyl-2-nitroimidazol-5-yl)-pyrrolidine-carboxy-p-anisidide in the form of an oily crude product. Recrystallization from ether yielded 2.5 g (27%) of pure product, m.p. 106-107°C; $[\alpha]_D^{25} = -66.5°$ (c = 1% in methanol).

Example 7

A lithium diisopropylamine solution (prepared from 65 ml of a 2.2 molar solution of butyl lithium in hexane and 14.5 g of diisopropylamine in 150 ml of tetrahydrofuran) was added dropwise at a temperature of −60°C within 15 minutes to a solution of 22 g of 1-methyl-2-nitroimidazole-5-methanol in 300 ml of tetrahydrofuran and 150 ml of dimethylformamide. The mixture was stirred at −60°C for 30 minutes and treated with 28 g of p-toluenesulphonyl chloride in 150 ml of tetrahydrofuran. After removing the cooling, warming to room temperature and adding 300 ml of ice/water, the mixture was extracted three times with 300 ml of ethyl acetate each time. The combined extracts were washed with 150 ml of saturated sodium chloride solution and evaporated under reduced pressure. The residue was purified on 800 g of silica gel with ethyl acetate/dichloromethane (1:3, v/v). After a forerun of 1.5 l, the next 1.5 l were collected and evaporated. Recrystallization from 70 ml of toluene yielded 12 g (50%) of 5-(chloromethyl)-1-methyl-2-nitroimidazole, m.p. 100-101°C.

2.9 ml of a 1.98 molar solution of sodium tert.amylate in toluene were added at −10°C to a solution of 1.26 g of 4'-hydroxy-1-pyrrolidine-acetanilide in 10 ml of dimethylformamide. 1 g of 5-(chloromethyl)-1-methyl-2-

nitroimidazole was subsequently added and the mixture was stirred at −10°C for 3 hours. 100 ml of water were added in order to isolate the product. Recrystallization of the product from 13 ml of acetonitrile yielded 0.42 g (21%) of α-(1-methyl-2-nitroimidazol-5-yl)-1-pyrrolidine-p-acetanisidide, m.p. 141-143°C.

Example 8

0.17 g of diethyl azodicarboxylate in 1.5 ml of tetrahydrofuran was added dropwise while cooling with ice and stirring strongly to a suspension of 0.14 g of 1-methyl-2-nitroimidazole-5-methanol, 0.22 g of 4'-hydroxy-1-pyrrolidine-acetanilide and 0.26 g of triphenylphosphane in 3 ml of absolute tetrahydrofuran. The mixture was stirred at room temperature for 3 hours and the resulting clear solution was evaporated under reduced pressure. The crude product was purified by chromatography on a silica gel column. Byproducts were firstly eluted with ethyl acetate, while the main product was obtained by elution with dichloromethane/methanol (9:1, v/v). Evaporation of the solvent mixture and crystallization from 1 ml of acetonitrile yielded 0.115 g (36%) of α-(1-methyl-2-nitroimidazol-5-yl)-1-pyrrolidine-p-acetanisidide, m.p. 140-142°C.

The following Examples illustrate pharmaceutical preparations containing the compounds of formula I and physiologically compatible acid addition salts thereof:

EXAMPLE A

Tablets

2-(Dimethylamino)-α-(1-methyl-2-nitro-imidazol-5-yl)-p-acetanisidide hydro-chloride	100 mg
Lactose	192 mg
Maize starch	80 mg
Hydrolyzed maize starch	20 mg
Calcium stearate	8 mg
	400 mg

EXAMPLE B

Tablets

α-(1-Methyl-2-nitroimidazol-5-yl)-1--pyrrolidine-p-acetanisidide hydro-chloride	50 mg
Lactose	194 mg
Pre-gelatinized maize starch	150 mg
Calcium stearate	6 mg
	400 mg

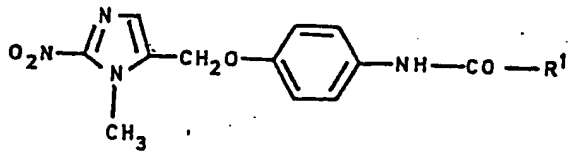
EXAMPLE C

Injection solution

2-(Dimethylamino)-α-(1-methyl-2-nitro-imidazol-5-yl)-p-acetanisidide		5.1 mg
Propylene glycol		0.4 ml
Benzyl alcohol (benzaldehyde-free)		0.015 ml
Ethanol (anhydrous)		0.10 ml
Sodium benzoate		48.8 mg
Benzoic acid		1.2 mg
Water (for injection)	q.s.	1.0 ml

CLAIMS

1. 2-Nitroimidazoles of the general formula



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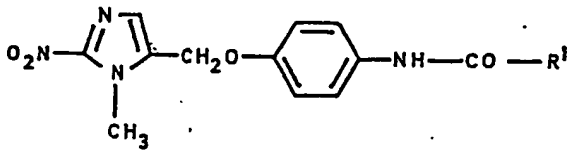
and physiologically acceptable acid addition salts thereof.

2. 2-Nitroimidazoles of the general formula



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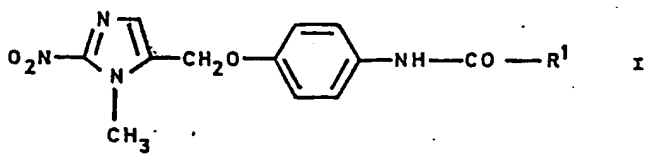
3. 1-Methyl-α-(1-methyl-2-nitroimidazol-5-yl)-pyrrolidine-carboxy-p-anisidide.
4. 2-(Dimethylamino)-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide.
5. 2-(Dimethylamino)-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide hydrochloride.
6. 2-(Diethylamino)-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide.
7. α-(1-Methyl-2-nitroimidazol-5-yl)-1-pyrrolidine-p-acetanisidide.
8. α-(1-Methyl-2-nitroimidazol-5-yl)-1-pyrrolidine-p-acetanisidide hydrochloride.
9. α-(1-Methyl-2-nitroimidazol-5-yl)-1-piperidine-p-acetanisidide.
10. α-(1-Methyl-2-nitroimidazol-5-yl)-4-morpholine-p-acetanisidide.
11. 2-Nitroimidazoles according to any one of claims 1-10 as medicaments.
12. 2-Nitroimidazoles according to any one of claims 1-10 as medicaments in veterinary medicine.
13. A process for the manufacture of 2-nitroimidazoles of the general formula



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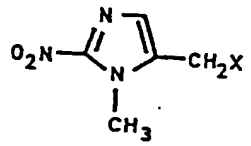
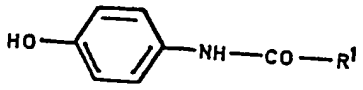
C_{1-4}-alkyl or $-NR^2R^3$ is the residue of a five-membered or six-membered saturated heterocyclic ring system which may contain a further nitrogen or oxygen atom in the ring,
and of physiologically acceptable acid addition salts thereof, which process comprises

(a) reacting a compound of the formula



II

wherein X represents hydroxy, chlorine bromine or iodine,
with a compound of the formula



III

or

(b) reacting a 2-halo-α-(1-methyl-2-nitroimidazol-5-yl)-p-acetanisidide with a compound of the formula HNR^2R^3 or

(c) reacting α-(1-methyl-2-nitroimidazol-5-yl)-p-anisidine with a compound of the formula R^1-COOH or a reactive derivative thereof and, if desired, converting a compound of formula I obtained into a physiologically acceptable acid addition salt.

14. Pharmaceutical preparations based on a compound according to any one of claims 1-10.
15. The use of a compound in accordance with any one of claims 1-10 as a medicament.
16. A compound in accordance with any one of claims 1-10 whenever prepared according to the process of claim 13 or by an obvious chemical equivalent thereof.
17. The invention as hereinbefore described.

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